

Increased morbidity odds ratio of primary liver cancer and cirrhosis of the liver among vinyl chloride monomer workers

Chung-Li Du, Jung-Der Wang

Abstract

Objectives—To determine if there is an increased risk of admission to hospital for various diseases among vinyl chloride monomer (VCM) workers.

Methods—2224 workers with occupational exposure to VCM were identified for occurrence of disease based on a search of hospital computer files on labour insurance. These data were compared with those of workers manufacturing optical equipment and motorcycles from 1 January 1985 to 31 March 1994. Cardiovascular and cerebrovascular diseases were used as reference diseases, and the age adjusted morbidity odds ratio (MOR) was calculated.

Results—A significantly increased risk of admission to hospital among VCM workers due to primary liver cancer (MOR 4.5–6.5), cirrhosis of the liver (MOR 1.7–2.1), and other chronic diseases (MOR 1.5–2.0) was found. There were eight cases of primary liver cancer, all with heavy previous exposure to VCM. Another four cases of hepatoma in polyvinyl chloride (PVC) workers were found in the death registry. Ten out of 11 cases of hepatoma, with detailed medical information, were carriers of hepatitis B virus. The average latent period (20 years) was not different from other studies. Alternative agents of primary liver cancer were largely ruled out, suggesting that the combination of hepatitis B and VCM may lead to primary liver cancer.

Conclusion—There is an increased risk of primary liver cancer in workers exposed to VCM, although the incomplete coverage of the Labor Insurance Bureau data warrants cautious interpretation of the results. Further study exploring the synergistic effects of VCM and hepatitis B is also indicated.

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osarcoma, lung cancer, brain cancer, haematopoietic cancer, etc.¹ Although these studies either consisted of followed up cohorts based on mortality or case reports, there has been relatively little epidemiological research directly involving morbidity. Although the morbidity odds ratio (MOR) study design was first proposed for use in cases of controlled study with both case and control series as decedents,² it is equally applicable for use in morbidity cases. The comprehensive coverage of labour insurance in Taiwan provides us with an excellent opportunity to use the MOR design for cases admitted to hospital with an industry specific exposure—such as VCM—which is commonly encountered in PVC or VCM production. The objective of this study was to determine if there is an increased risk of admission to hospital for various diseases among VCM workers.

Methods

The study population was recruited from workers at five domestic PVC factories, during the period of 1989–95, based on health examinations including five liver function tests and a detailed interview of the workers' occupational and medical histories. There were 714 current workers. The data for former PVC workers were collected from the Labor Insurance Bureau, which is operated by the government of Taiwan and keeps a comprehensive record of any change in employees' insurance status. The Labor Insurance Bureau contains data on basic demographic information of workers in each PVC company, including citizen identification number, date of birth, sex, insurance starting date, any change of salary or factory, insurers department record, job title, etc, although contents of the insurers department record and job title are usually considered void. We were able to collect 1575 former workers exposed to VCM from all PVC factories who had jobs—such as polymerisation, drying, storage and transportation, machine maintenance, etc. In total, 2289 current and former workers were enrolled. Among them, 2224 workers (97%) could be identified by their identification numbers and were treated as the exposed group.

We used the exposed workers' identification numbers and Labor Insurance Bureau computer files on admission to hospital to find the cause of admission to any hospital in Taiwan during the period of 1 January 1985 to 31 March 1994. To ensure a consistent time scale, we restricted the data of the exposed group to

Institute of Occupational Safety and Health, Council of Labor Affairs, Executive Yuan, Taipei, Taiwan
C-L Du

Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan
C-L Du
J-D Wang

Correspondence to:
Dr Jung-Der Wang, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health No 1, Sec 1, Jen-Ai Road, Taipei, Taiwan.

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Vinyl chloride monomer (VCM) is the raw material of polyvinyl chloride (PVC), a useful plastic. Since 1974 when the first case of angiosarcoma of the liver was diagnosed in VCM workers in the United States, there have been several studies documenting an increased risk of mortality among PVC workers due to angio-

Table 1 Case number of vinyl chloride monomer (VCM) workers admitted to hospitals for various diseases from 1 January 1985 to 31 March 1994, compared with optical workers and motorcycle manufacturers (the non-exposed populations) and cardiovascular-cerebrovascular (CV-CB) diseases (the reference diseases)

Cause of morbidity	VCM workers	Optical workers	Motorcycle manufacturers
Workers admitted to hospital (n)	1044	3667	5861
Primary liver cancer	8	9	9
Chronic liver disease and liver cirrhosis	35	89	180
Chronic respiratory disease	38	118	298
Haematopoietic cancer	4	7	10
Stomach cancer	2	8	6
Respiratory cancer	3	8	15
All accidental injuries	350	1213	3173
Occupational injuries	221	269	1471
All other chronic diseases	159	599	708
CV-CB diseases	40	180	288

those who were admitted after working in the PVC industry. Admission to hospital files contained the hospital code, industry code, identification number, age, sex, the reason for disease upon admission, date and period of admission, and all medical charges. The standard industrial classification (SIC) code was adopted from the Directorate-General of the Budget, Accounting and Statistics of the Executive Yuan, and was directly translated from the international standard industrial classification with only minor modifications. The SIC code of the Labor Insurance Bureau files had four digits. The first digit indicated one of nine large industrial sectors; the four digits contained more than 600 subcategories. To assure comparability of contrasted populations for the MOR study, we deliberately selected reference populations from occupations with similar wages but without exposure to VCM or other known hepatotoxic agents. Thus, we selected our reference population to be workers who manufactured or assembled optical equipment and instruments (SIC category no 3802), and who produced motorcycle parts and accessories (SIC category no 3704). The reason for admission to hospital was coded according to the international classification of diseases, ninth revision (ICD-9). All reasons for admission to hospital, except accident or acute conditions, were only counted once if there were several instances of admission related to a specific cause. However, a person might also be admitted to hospital for more than one disease. In this study, we tried to explore cancers, cirrhosis of the liver, non-malignant pulmonary diseases, and accidental injuries.

We selected admission to hospitals due to cardiovascular or cerebrovascular diseases, which include rheumatic heart disease, hypertension, ischaemic heart disease, cor pulmonale, and cerebral vascular diseases as the reference diseases. After finding the number of workers in different disease categories, workers were also stratified by age on admission. Then the age adjusted MOR and the corresponding 95% confidence interval (95% CI) were established with multiple logistic regression on the SAS package, 6.08 edition.³ Also, to verify the cause of liver cancer, patients with a diagnosis of primary liver cancer were further researched by examining their original hospital medical records. These records were identified by linking the hospital codes. Clinical details were obtained with the aid of responsible doctors in each specific hospital.

Results

There was a total of 1058 patients admitted to hospitals in the PVC group during the period 1 January 1985 to 31 March 1994, a total follow up period of 9.33 years. Only 14 female patients from the PVC group were admitted to hospital. As none of these women were admitted for cirrhosis of the liver or cancer, we excluded all female patients. Moreover, 3667 male optical workers and 5681 male motorcycle workers were also admitted to hospital. Table 1 shows the frequency distribution for various admissions for disease or injury among the male PVC group (optical workers and motorcycle workers). After adjustment for age at occurrence of disease, the PVC workers were found to have significantly increased risks of admission to hospital due to primary liver cancer (MOR 4.5–6.5). Table 2 shows that there was a less significant increase for cirrhosis of the liver (MOR 1.7–2.1) and other chronic diseases (MOR 1.5–2.0), compared with both reference groups of optical and motorcycle manufacturers. There were significantly increased MORs for haematopoietic cancer, chronic respiratory disease, and accidental injury compared with only one reference group. Table 3 shows that the eight cases of primary liver cancer were all diagnosed as hepatoma or hepatocellular carcinoma.

Discussion

The method adopted in our study—that is, an MOR design—is not as straightforward as the

Table 2 Logistic regression models with OR (95% CI) for vinyl chloride monomer (VCM) workers admitted to hospitals for various diseases from 1 January 1985 to 31 March 1994, compared with optical workers and motorcycle (motor) manufacturers (the non-exposed populations) and cardiovascular-cerebrovascular diseases (the reference diseases) (ORs were adjusted for age at first admission)

Cause of morbidity	VCM v Motor	VCM v Optical	Effect of age		
			<40 v 40–50*	<40 v >50	
Primary liver cancer	6.5 (2.3 to 18.4)	4.5 (1.5 to 13.3)	1.1 (0.4 to 3.0)	1.4 (0.5 to 4.0)	
Haematopoietic cancer	3.4 (1.0 to 11.8)	3.1 (0.8 to 11.8)	2.4 (0.9 to 6.7)	18.1 (2.3 to 138.4)	
Stomach cancer	2.2 (0.4 to 11.0)	1.0 (0.2 to 5.1)	0.3 (0.1 to 2.0)	0.3 (0.1 to 1.3)	
Respiratory cancer	1.4 (0.4 to 5.1)	1.6 (0.4 to 6.4)	0.8 (0.3 to 2.7)	1.1 (0.4 to 2.9)	
Chronic liver disease and liver cirrhosis	1.7 (1.0 to 2.6)	2.1 (1.2 to 3.7)	<35 v 35–45	<35 v 45–55	<35 v >55
Chronic respiratory disease	1.2 (0.8 to 2.0)	2.1 (1.2 to 3.5)	1.7 (0.6 to 4.8)	3.8 (2.5 to 5.7)	9.0 (5.3 to 15.3)
Other chronic disease	2.0 (1.4 to 2.8)	1.5 (1.0 to 2.3)	2.6 (1.8 to 3.8)	4.8 (3.2 to 7.0)	2.7 (1.9 to 3.9)
Accidental injury	1.4 (0.9 to 2.0)	2.3 (1.6 to 3.4)	2.5 (1.8 to 3.3)	4.5 (3.4 to 6.0)	7.5 (5.5 to 9.9)
			4.3 (3.4 to 5.9)	9.4 (7.2 to 12.3)	15.0 (11.3 to 19.7)

*Age (y) at first admission.

Table 3 The basic data and diagnostic variables of workers exposed to vinyl chloride monomer (VCM) admitted due to primary liver cancer

Case No	Major work history	Duration from first exposure (y)	Age at admission (y)	Major clinical image finding	Pathology or cytology report	HBs Ag	Anti-HCV	Alcoholism history	Cirrhosis of liver
1	VCM shipping	8.0	53	Sonography: cirrhosis, right lobe tumour, portal vein thrombi, AFP=7590 µg/l	(-)	(+)	(-)	NA	(+)
2	Polymerisation	25.1	51	CT: tumour mass with central necrosis, metastasis post wedge resection	Pathology: HCC	(+)	NA	(-)	(-)
3	Polymerisation	14.5	43	Sonography performed	Cytology: HCC	(+)	NA	(-)	(+)
4	VCM shipping and polymerisation	21.5	47	CT: right lobe hepatoma, mild hepatomegaly	(-)	(-)	NA	NA	(+)
5	Polymerisation	18.9	47	CT: right lobe hepatoma, cirrhosis, splenomegaly	Cytology: HCC	(+)	NA	(-)	(+)
6	Polymerisation	25.6	51	CT and angiography: right lobe hepatoma, portal vein thrombi	(-)	(+)	(-)	(-)	(+)
7	Polymerisation	12.3	51	Liver scan: multiple space-occupying lesion, portal vein occlusion, AFP=9000 µg/l	Necrotic tissue noted only	(+)	NA	(+)	NA
8	Polymerisation	13.2	47	Sonography: multiple hepatoma with bone metastasis	(-)	(+)	NA	(-)	(+)
9*	Public utility	28.0	64	CT:multiple hepatoma over right lobe, AFP=16698 µg/l	Pathology: HCC	(+)	NA	(-)	(-)
10*	Maintainance	29.1	68	Sonography: hepatoma	NA	(+)	NA	NA	NA
11*	Polymerisation	27.9	57	Sonography: right lobe hepatoma	NA	NA	NA	NA	(+)
12*	Loading or unloading VCM	15.8	41	Sonography:1.5 cm mass over left liver with ascites, AFP=3.0 µg/l	NA	(+)	NA	(+)	(+)

*Additional cases found from death certificates.

CT=computed tomography; AFP= α -fetoprotein; HCC=hepatocellular carcinoma; HBsAg=hepatitis B surface antigen; anti-HCV=hepatitis C virus antibody; NA=data unavailable.

Table 4 One year hospital admission rates of cardiovascular-cerebrovascular (CV-CB) diseases in workers in petrochemical material, fine equipment and transportation vehicle manufacturing (data were abstracted from 1988 statistics from the Labor Insurance Bureau)

	Age stratum (y)	Petrochemical materials	Fine equipment	Transportation vehicles
Cases admitted to hospital because of CV-CB disease	<45	30	71	278
	≥45	165	55	371
Insured population	<45	34761	15448	76750
	≥45	10204	2724	16864
Rate of admission to hospital / 100000	<45	374	362	460
	≥45	1617	2190	2020

traditional SMR (standardised mortality ratio). But as it was too difficult to reconstruct the past working history of each cohort member, owing to poor detailed occupational histories of individual companies, we were unable to launch a comprehensive SMR study at the present time. Nonetheless, in our MOR study with a case-control design, we have selected only diseases known to be unrelated to the exposure to strengthen the validity of our estimate.⁴ Namely, we deliberately ruled out chronic liver disease, acro-osteolysis and other cancers, and instead chose cardiovascular and cerebrovascular diseases as the reference diseases. Thus, significantly less bias should be involved in the calculation of the observed to expected ratio. Moreover, as we selected reference occupations of the same socioeconomic status, indicating similar patterns of smoking and drinking, these factors were not likely to act as confounders.^{5 6}

However, there is still considerable possibility of selection bias: are there different forces of entry into and exit from the exposed and non-exposed populations in the Labor Insurance Bureau data? In Taiwan, all factories employing more than five workers were automatically required to join the Labor Insurance Bureau, and workers under such insurance were then free to choose their doctor and hos-

pital free of charge. Although workers could only choose from hospitals under contract to the Labor Insurance Bureau, about 78.4% of all hospitals in Taiwan in 1992 had such a contract. Thus, the likelihood of selection bias between these two populations was low before retirement. After retirement, workers had themselves to pay for any medical service. Therefore, there might have been a possible differential bias after retirement according to different incomes. But as we chose two reference populations with similar incomes to those of VCM workers, there should be relatively little bias. To evaluate the completeness of the Labor Insurance Bureau data, we matched the 2224 workers without liver cancer with our National Mortality Registry from 1 January 1985 to 31 March 1994 and found that 41 of them had died. Four more fatal cases of primary liver cancer were found in the death registry. After verification by original death certificates and corresponding hospital codes, we were able to obtain detailed clinical information for three of the four (table 3). Among all four, cases nine and 10 were diagnosed eight years after retirement, case 11 left the Labor Insurance Bureau in 1989 and died three months later, and case 12 was diagnosed with hepatoma at a non-insurance hospital. Assuming that latency period of

primary liver cancer had been correctly assessed and only workers employed before 1 January 1985 had fulfilled the selection criteria, the total number of workers was 1887 and cases of primary liver cancer numbered 11, bringing the total incidence of primary liver cancer in VCM workers in Taiwan to be about $11/(1887-1/2 \times (41+8)) \times 9.33=63.3/100\ 000$ people on average per year during the study period. This rate is higher than the crude incidence of male primary liver cancer, which is 28.4 per 100 000 people,⁷ according to Taiwan's Cancer Registry Report, 1994.

Patients with primary liver cancer consisted of three primary groups: hepatocellular carcinoma originating from hepatocytes (which comprised the majority), cholangiocarcinoma stemming from the bile duct, and angiosarcoma arising from the endothelial lining. In this study, adding the clinical data of the four mortality cases and eight morbidity cases together, we had 12 cases of primary liver cancer. Among them, four were confirmed to be hepatocellular carcinoma by histology, and two additional cases had extremely high concentrations of α -fetoprotein (AFP). It has been well accepted that an AFP concentration of $>1000\ \mu\text{g/l}$, in an adult, with liver disease, and without an obvious gastrointestinal tract tumour, strongly suggests the presence of hepatocellular carcinoma.⁸ Whereas, in cases with angiosarcoma of the liver, at least one study reported that none of its patients had an increased concentration of AFP.⁹ Therefore, we considered these two cases to be hepatocellular carcinoma. Of the remaining six cases, four were carriers of hepatitis B surface antigen (HBsAg). Although they were diagnosed as hepatoma or hepatocellular carcinoma, the possibility of angiosarcoma of the liver could not be completely excluded because these two kinds of malignant liver neoplasm are difficult to distinguish based solely on imaging study or clinical signs and symptoms without any pathological confirmation. Thus, we had six cases of hepatocellular carcinoma and six of primary liver cancer in the study. All 12 of these workers were employed before the first year (1985) of follow up, and at the time, they faced heavy exposure to VCM while working. They had an average working duration of 5–30 years and an average duration from first exposure to the occurrence of primary liver cancer of 20 years, with a range of 8.0 to 29.1 years, which is similar to other studies.^{9–11} In general, the longer the latency period, the greater the risk of developing cancer. This seems to be true for developing primary liver cancer after exposure to VCM.^{12–13} We expect that in the coming years, there will be a higher incidence of primary liver cancer among VCM workers in Taiwan because most workers were employed after 1970.

Although we found that exposure to VCM was associated with both a higher odds ratio and a higher incidence of liver cancer, we must still rule out other alternative aetiological agents, including hepatitis B¹⁴ and C¹⁵ viruses, smoking,¹⁶ alcohol consumption,¹⁷ aflatoxins,¹⁸ arsenic,¹⁹ pesticides, asphalt,²⁰ etc. In this study,

as we deliberately chose optical and motorcycle manufacturing workers, who earned similar wages to those of PVC workers, the likelihood of different patterns or distributions of smoking, drinking, or dietary intake of aflatoxin should be low. For the reference diseases, we found that one year hospital admission rates for cardiovascular and cerebrovascular disease in workers in the manufacture of petrochemical material, fine equipment, and vehicles were similar in 1988 (table 4).²¹ A review of the residential areas and previous work histories of these workers with primary liver cancer also showed that none of them came from black foot endemic areas where the arsenic content of drinking water was high, and none ever held a job involving exposure to asphalt or pesticides. Moreover, there was no known restriction on selecting or dismissing workers based on his or her hepatitis B or C status in Taiwan. The likelihood of different proportions of hepatitis B and C between the exposed and reference populations should also be low. Although we did not have any information on the prevalence of HBsAg and antibodies to hepatitis C (anti-HCV) among the reference populations, annual physical examinations of the PVC workers over the five-year study period showed that the prevalence of HBsAg carriers was 19.3%, whereas workers >40 years old from one big motorcycle manufacturing company had a 16.9% (118/698) rate of carrying hepatitis B, and workers >45 years old in one big optical equipment manufacturing factory had a 14.3% (34/238) rate of carrying hepatitis B. All the results were close to the average nationwide prevalence of 15%–20%.^{22–23} The anti-HCV prevalence in PVC workers was 1.6%, which was also within the range of the general population, at 1%–4%.^{24–25} Earlier data on anti-HCV were not available because anti-HCV examinations were not done before 1992. In this study, we found the percentage of hepatitis B carriers among these cases of primary liver cancer (91%, 10/11) to be higher than in other studies (77%–86%).^{22–26–27} Although the number of cases was small, it raises concern that the rate of HBsAg carriers among PVC workers with primary liver cancer may be higher than that of the general population with hepatoma. Hepatitis B infections have been found to have synergistic effects with chemicals such as alcohol²⁸ and dimethyl formamide²⁹ in producing liver damage and liver cancer. Moreover, one study found in healthy HBsAg carriers an increased cytochrome P-450 dependent function,³⁰ which may more readily activate peroxide metabolites of VCM. It is possible an HBsAg carrier may also be prone to a combined carcinogenic effect of hepatitis B and VCM. Future follow up studies of VCM workers with HBsAg is indicated to help determine the mechanisms responsible.

Vinyl chloride monomer has been shown to be a multipotential carcinogen in animals.³¹ In humans, a causal relation has been found between occupational exposure to VCM and angiosarcoma of the liver. It was not until 1983 that Evans *et al* reported two cases of

hepatocellular carcinoma among VCM workers.³² Later on, several epidemiological studies (in the United States¹² and Europe^{10,13}) also corroborated such an association in humans. According to recent experimental studies performed by Froment *et al.*, different molecular mechanisms of exposure to VCM may lead to different cell types of liver tumour, including angiosarcoma of the liver and hepatocellular carcinoma.³³ No data on viral hepatitis markers, however, are available from these studies. Thus, we are among the first to report such a high incidence of primary liver cancer or hepatocellular carcinoma among VCM workers, and the possible synergistic influence of viral hepatitis deserves more attention.

Based on a literature review, prolonged exposure to VCM has also been reported to be the cause of abnormal liver function tests, liver fibrotic changes, and splenomegaly.^{34,35,36} We also found a mild increase in chronic liver disease or cirrhosis among VCM workers. It is consistent with an increased odds ratio of primary liver cancer, which is usually the consequence of chronic liver hepatitis or cirrhosis. In our study, PVC workers also had a higher percentage of occupational injuries among accidental injuries compared with the reference groups, suggesting that the mid-stream petrochemical industry in Taiwan had a higher rate of occupational hazards. Most cases with hepatocellular carcinoma or primary liver cancer were involved in the polymerisation process, which usually entailed the extremely high exposure tasks of autoclave cleaning and tank cleaning³⁷ in the early years. Three patients with primary liver cancer were involved in VCM shipping and two worked mainly in the public utility or maintenance, suggesting the possibility of high exposure of workers to VCM in the shipping and storage processes. Therefore, workers deserve an improved exposure control for all of these processes.

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